REMARKS

Claims 83, 90, 118, 129, 130, 140, 141, 142, 149, 150 and 157 are pending in the application.

No new matter has been added by the amendments submitted herein, as explained further below.

Specification

Applicant requests that the attached paper copy of the Sequence Listing be entered into the application in place of the current paper copy of the Sequence Listing. The attached paper copy is identical to the computer readable form on file.

Claim Objections

Claims 158 to 161 have been deleted rendering moot any objection thereto.

Allowable Subject Matter

As set out further below, the claims have been amended in view of the Examiner's position that claims drawn to a microsomal preparation comprising a polypeptide having the amino acid sequence of SEQ ID NO:2 or a sequence that is at least 95% identical to SEQ ID NO:2 and a polypeptide encoded by SEQ ID NO:3 or sequence that hybridizes to SEQ ID NO:3 under highly stringent conditions are allowable.

Claim Rejections - 35 USC § 112

Claims 83 and 90 have been rejected because of the limitation "wherein the microsomal preparation is substantially free of other proteins that are cytochromes expressed by epidermal cells", it being alleged that this limitation does not enjoy adequate support by the disclosure. Applicants respectfully disagree with this allegation as support for this limitation is provided by Figure 13(a) but the limitation has nonetheless been deleted to advance prosecution of this application.

It has been alleged that the limitation "wherein the amino acid sequence identity between the protein and SEQ ID NO:4 is at least about 93 percent" does not enjoy adequate support by the disclosure. Applicants respectfully disagree with this allegation as support for this limitation is provided at the end of the first paragraph of the "Discussion" section of the specification as filed, but the limitation has nonetheless been deleted to advance prosecution of this application.

Claims 158 to 161 have been rejected, it having been alleged that limitations of "wherein the preparation is enriched at least 6.3 fold in said oxidase activity with respect to a microsomal preparation obtained from a non-transfected said cell under the same conditions" and "wherein the preparation is enriched at least 7.8 fold in said hydroxylase activity with respect to a microsomal preparation obtained from a non-transfected said cell under the same conditions" do not enjoy adequate support by the disclosure. Applicants respectfully disagree with these allegations, but all claims reciting these limitations have nonetheless been deleted to advance prosecution of this application.

Claims 116, 120 to 128, 131 to 139, 142 to 147, 149 to 155, 157, 160 and 161 stand rejected for lacking enablement commensurate with their scope. The most recent action acknowledges that the specification is enabling at least for an all-*trans* retinoic acid 4-hydroxylase encoded by SEQ ID NOs: 3, 5 or 31 or a sequence that hybridizes

thereto under highly stringent conditions as well as for an all-*trans* retinoic acid 4-hydroxylase having the amino acid sequence of SEQ ID NOs: 2, 4 or 32 or a sequence that is at least 95% identical thereto. All claims requiring the presence of protein now respectively require the protein to be: (i) encoded by a nucleic acid molecule, wherein said protein oxidizes all-*trans* retinoic acid at the C4-position of the ß-ionone ring, said nucleic acid molecule comprising a nucleotide sequence that hybridizes under high stringency conditions, wherein high stringency conditions include a wash step of about 0.2 x SSC at 65°C, to a polynucleotide having a nucleotide sequence (claim 83); (ii) encoded by a nucleic acid molecule, wherein said protein hydroxylates all-*trans* retinoic acid at the C4-position of the ß-ionone ring, said nucleic acid molecule comprising a nucleotide sequence that hybridizes under high stringency conditions, wherein high stringency conditions include a wash step of about 0.2 x SSC at 65°C, to a nucleic acid molecule having a nucleotide sequence (claim 90); (iii) encoded by a nucleic acid molecule, wherein said protein oxidizes all-*trans* retinoic acid at the C4-position of the ß-ionone ring, said nucleic acid molecule encoding an amino acid sequence that is at least 95 percent conserved with respect to SEQ ID NO:2 (claim 142); or (iv) encoded by a nucleic acid molecule, wherein said protein hydroxylates all-*trans* retinoic acid at the C4-position of the ß-ionone ring, said nucleic acid molecule encoding an amino acid sequence that is at least 95 percent conserved with respect to SEQ ID NO:2 (claim 150). Applicants believe that these amendments render the rejection moot.

Claims 83, 90, 142 and 150 stand rejected for lack of clarity. The amendment suggested by the Examiner for each of these claims has been incorporated into each of these claims, rendering this rejection moot.

Claims 116, 120 to 128, and 131 to 139, rejected as indefinite, have been cancelled, rendering this rejection moot.

Claim 130 stands rejected as indefinite for requiring that the recited protein be capable of hydroxylating the C18-position of all-*trans* retinoic acid while being dependent from a claim which requires the protein to be capable of oxidizing all-*trans* retinoic acid at the C4-position of the ß-ionone ring. Applicants respectfully disagree with the allegation that this claim is indefinite, but nonetheless have amended the claim by inserting the word "additionally" in front of the word "hydroxylates". The activity of the protein of the parent claim is not confined to the activity recited in that claim. Claim 130 is narrower in scope than the claim from which it depends in requiring the protein to have both recited activities. Withdrawal of this rejection is respectfully requested.

Claims 141, 149 and 157 have been similarly rejected. These claims have been amended similarly to claim 130, and for analogous reasons, withdrawal of the rejections of claims 141, 149, and 157 is respectfully requested.

Claim Rejections - 35 USC § 103

All claims reciting SEQ ID NOs: 4, 5, 31 and 32 have been cancelled, rendering rejections made on this basis moot.

Applicants, however, do not accept that any of the claims are in fact rendered obvious by any of the prior art of record. None of the prior references discloses or renders obvious amino acid sequences shown by SEQ ID NO:4 or 32, or their coding sequences, despite the possible presence of a protein having SEQ ID NO:4 in the crude preparations of Duell *et al.*

Further, as set out in Applicants' previous response, all of the Duell *et al.* references describe expression of a protein in epidermal cells only and the expression must be induced by exposure of those cells to retinoic acid. This is much different from Applicants' invention which, through the use of transfection, provides expression of a

specific protein without the presence of other cytochromes normally present in skin cells. Moreover, induction of biological activity of this protein by retinoic acid is not required in the transfected cells. An advantage of Applicants' invention as claimed is, for example, in the area of screening drugs (page 9, line 26 to line 40 of the application as filed), where certainty of the identity and presence of the protein being targeted is reproducibly provided, absent contaminating proteins and activities normally present in skin cells. None of the preparations of Duell *et al.* can provide this certainty. While it might be true that cells obtained from other tissues, e.g., liver, would be substantially free of proteins normally expressed by epidermal cells, preparations obtained from the cells of another such tissue would contain other proteins normally expressed by such tissue and therefore suffer the analogous limitations as preparations obtained from epidermal cells. Without the ability to obtain cells via transfection, the skilled person is simply not enabled to reproducibly obtain the targeted protein with certainty.

All amendments made herein have been made solely to advance prosecution of this application unless otherwise indicated, and Applicants reserve the right to file a continuation or other application as appropriate in order to address otherwise outstanding issues.

Applicants believe that all of the issues addressed in the outstanding Action have been addressed in this response, and thus request allowance of the application.

In the event that any issue remains, or if the Examiner is disposed to issue an unfavorable advisory action, the Examiner is invited to telephone the undersigned at (416) 865-8121.

A petition for extension of time for submitting this response, and an authorized Visa Credit Card, Form PTO 2038 accompany this response. Applicants hereby request any further extension of time that may be necessary. Please charge any additional fees

which may be required for the papers being filed with this letter to our authorized Visa Credit Card. In the event that charges cannot be made to the authorized credit card, please charge any fee to Deposit Account No. 502651.

Yours very truly,

June 22, 2004
Date

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